PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference PC32574A	FOR FURTHER ACTION	See Form PCT/IPEA/416
International application No. PCT/IB2004/003063	International filing date *(day/month/year)* 14.09.2004	Priority date *(day/month/year)* 19.09.2003
International Patent Classification (IPC) or national classification and IPC A61K31/192, A61K31/216, A61K31/455, A61K38/00		
Applicant PFIZER HEALTH AB		

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 8 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. ☒ *sent to the applicant and to the International Bureau)* a total of 4 sheets, as follows:
      ☐ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.
   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in computer readable form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).

4. This report contains indications relating to the following items:

☒	Box No. I	Basis of the opinion
☐	Box No. II	Priority
☒	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☐	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☒	Box No. VI	Certain documents cited
☐	Box No. VII	Certain defects in the international application
☐	Box No. VIII	Certain observations on the international application

Date of submission of the demand	Date of completion of this report
03.11.2004	14.02.2006
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized Officer Kling, I Telephone No. +49 89 2399-8471

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/IB2004/003063

Box No. I Basis of the report

1. With regard to the **language**, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This report is based on translations from the original language into the following language , which is the language of a translation furnished for the purposes of:
   - ☐ international search (under Rules 12.3 and 23.1(b))
   - ☐ publication of the international application (under Rule 12.4)
   - ☐ international preliminary examination (under Rules 55.2 and/or 55.3)

2. With regard to the **elements*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

Description, Pages	
1-40	as originally filed
Claims, Numbers	
1-29	received on 27.05.2005 with letter of 26.05.2005
Drawings, Sheets	
1/19-19/19	as originally filed

   ☐ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing

3. ☐ The amendments have resulted in the cancellation of:
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

* *If item 4 applies, some or all of these sheets may be marked "superseded."*

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 1-13

because:

☒ the said international application, or the said claims Nos. 1-13 relate to the following subject matter which does not require an international preliminary examination (specify):

see separate sheet

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the said claims Nos.

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form	☐	has not been furnished
	☐	does not comply with the standard
the computer readable form	☐	has not been furnished
	☐	does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See separate sheet for further details

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/IB2004/003063

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-29
	No:	Claims	
Inventive step (IS)	Yes:	Claims	1-29
	No:	Claims	
Industrial applicability (IA)	Yes:	Claims	14-29
	No:	Claims	1-13 (see item III)

2. Citations and explanations (Rule 70.7):

see separate sheet

Box No. VI Certain documents cited

1. Certain published documents (Rule 70.10)

and / or

2. Non-written disclosures (Rule 70.9)

see separate sheet

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

Claims 1 to 13 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

For the assessment of the present claims 1 to 13 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

Reference is made to the following documents:

D1: NIELSEN S ET AL: "EFFECTS OF LOWERING CIRCULATING FREE FATTY ACID LEVELS ON PROTEIN METABOLISM IN ADULT GROWTH HORMONE DEFICIENT PATIENTS" GROWTH HORMONE AND IGF RESEARCH, CHURCHILL LIVINGSTONE, LONDON,, GB, vol. 12, no. 6, 2002, pages 425-433, XP008024364 ISSN: 1096-6374

D2: SEGERLANTZ M ET AL: "INHIBITION OF THE RISE IN FFA BY ACIPIMOX PARTIALLY PREVENTS GH-INDUCED INSULIN RESISTANCE IN GH-DEFICIENT ADULTS" JOURNAL OF CLINICAL ENDOCRINOLOGY AND METABOLISM, NEW YORK, NY, US, vol. 86, no. 12, 2001, pages 5813-5818, XP001172852 ISSN: 0021-972X

D3: EP-A-1 186 293 (PFIZER PROD INC) 13 March 2002 (2002-03-13)

D4: US 2001/041673 A1 (FOSSA ANTHONY A) 15 November 2001 (2001-11-15)

D5: DATABASE BIOSIS [Online] BIOSCIENCES INFORMATION SERVICE, PHILADELPHIA, PA, US; December 2003 (2003-12), SEGERLANTZ MIKAEL ET AL: "Inhibition of lipolysis during acute GH exposure increases

insulin sensitivity in previously untreated CH-deficient adults." XP002314344 Database accession no. PREV200400102066

The present application meets the criteria of Article 33(1) PCT, because the subject-matter of claims 1 to 29 is novel in the sense of Article 33(2) PCT.

Document D1 discloses the effects of lowering circulating free fatty acid levels on protein metabolism in adult growth hormone deficient patients. The study was conducted to define the roles of lowering circulating free fatty acids (FFA) and of growth hormone (GH) replacement on protein metabolism in GH deficient patients. To isolate the specific effects of FFA and GH they studied seven adult subjects with GH deficiency four times: (A) with administration of GH and Acipimox (an inhibitor of lipolysis), (B) with GH, without Acipimox, © without GH, with Acipimox and (D) without either. Overall, They saw no intervention effect on protein metabolism, but when the two situations in which Acipimox was given were combined, Acipimox decreased basal plasma FFA concentrations by 75% and increased serum urea concentrations by 20%, whole body appearance rates (reflecting protein degradation) of phenylalanine (by 7%) and tyrosine (by 11%) and protein synthesis rates for phenylalanine (by 7%), whereas phenylalanine-to-tyrosine conversion was unaffected. Acipimox more than doubled net forearm phenylalanine release during the clamp and increased basal forearm phenylalanine disappearance (reflecting muscle protein synthesis). During the clamp whole body amino acid fluxes and phenylalanine-to-tyrosine conversion decreased together with a decrease in forearm protein breakdown.

D1 does neither refer to a juvenile population nor to any growth promoting effect.

In contrast the present application relates to the use of growth hormone in combination with at least one free fatty acid regulator to treat a growth disorder in a juvenile and to the use of at least one free fatty acid regulator to increase the growth promoting effect of GH therapy in a juvenile. Indeed as stated in claims 1 and 2 the present application pursued in both claims relate to growth promotion in juvenile populations and NOT in adult population.

D2 relates to test the hypothesis that GH-induced insulin resistance is mediated by an increase in FFA levels we assessed insulin sensitivity after inhibiting the

increase in FFA by a nicotine acid derivative, Acipimox, in nine GH-deficient adults receiving GH replacement therapy. The patients received in a double blind fashion either Acipimox (500 mg) or placebo before a 2-h euglycemic (plasma glucose, 5.5 +- 0.2 mmol/liter) hyperinsulinemic (serum insulin, 28.7 +- 6.3 mU/liter) clamp in combination with indirect calorimetry and infusion of [3-<3>H]glucose. Acipimox decreased fasting FFA by 88% (P = 0.012) and basal lipid oxidation by 39% (P = 0.015) compared with placebo. In addition, the insulin-stimulated lipid oxidation was 31% (P = 0.0077) lower during Acipimox than during placebo. Acipimox increased insulin-stimulated total glucose uptake by 36% (P = 0.021) compared with placebo, which mainly was due to a 47% (P = 0.015) increase in glucose oxidation. GH induced insulin resistance is partially prevented by inhibition of lipolysis by Acipimox.
D2 does neither describe the use of a FFA regulator to prevent/to treat any adverse consequence of GH treatment in a juvenile population as stated in claim 3 nor discloses the use of a FFA regulator to prevent /treat oedema induced by GH treatment as stated in claim 4 or trabecular bone loss associated with early GH therapy as stated in claim 5: The subject-matter of claims 3 to 5 is novel over the teaching of D2.

Inventive step

D3 discloses that a growth hormone secretagogue can also be used in combination with a compound useful to treat insulin resistance. Representative agents that can be used include insulin and insulin analogs; antilipolytic agents: nicotinic acid, acipimox, WAG 994. Also contemplated for use in combination with a growth hormone secretagogue are pramlintide acetate (Symlin TM), AC2993, and nateglinide.
There is no mention or suggestion of using GH in combination with any of these agents. In addition the indications of interest concern adult populations whereas the present invention targets pediatric indications, i.e. growth disorders in juveniles, promotion of growth in juveniles or prevention or treatment of GH-induced adverse events in juveniles. In addition, there is no reference to the treatment of oedema or trabecular bone loss associated with early stages of GH therapy using any of the combinations described in D3.

D4 is directed to pharmaceutical compositions comprising corticotrophin releasing factor antagonist and growth hormone or growth hormone secretagogues, to treat

or prevent osteoporosis or obesity, musculoskeletal frailty, congestive heart failure or insulin resistance, accelerating bone fracture repair, attenuating protein catabolic response after a major operation, reducing cachexia and protein loss due to chronic illness, accelerating wound healing, or accelerating the recovery of burn patients or of patient having undergone major surgery. D4 does not disclose or suggest the use of GH in combination with a free fatty acid regulator to treat any of the condition described in the present application. In addition there is no reference to treatment or prevention of oedema or trabecular bone loss associated with GH therapy using any of the combinations described in D4.

The present application meets the criteria of Article 33(1) PCT, because the subject-matter of claims 1 to 29 involves an inventive step in the sense of Article 33(3) PCT.

Re Item VI

Certain documents cited

The current assessment is based on the assumption that all claims enjoy priority rights from the filing date of the priority document. If it later turns out that this is not correct, the document D5 cited in the international search report could become relevant to assess whether claims 1 to 29 satisfy the criteria set forth in Article 33(1) PCT.

CLAIMS

1. A method of treating a growth disorder in a juvenile, said method comprising administering to said juvenile an effective amount of at least one FFA regulator in combination with growth hormone.

2. A method of increasing the growth promoting effects of growth hormone therapy in a juvenile, said method comprising administering an effective amount of at least one FFA regulator in combination with growth hormone.

3. A method of preventing or treating an adverse consequence of growth hormone treatment in a juvenile, comprising administering an effective amount of at least one FFA regulator in combination with said growth hormone treatment.

4. A method of preventing or treating oedema as an adverse consequence of growth hormone treatment in a mammal, comprising administering an effective amount of at least one FFA regulator in combination with said growth hormone treatment.

5. A method of preventing or treating trabecular bone loss associated with early stages of GH therapy as an adverse consequence of growth hormone treatment in a mammal, comprising administering an effective amount of at least one FFA regulator in combination with said growth hormone treatment.

6. The method of anyone of claims 3 to 5, wherein said mammal or juvenile suffers from a growth disorder.

7. The method of any of the preceding claims, wherein said juvenile or said mammal is human.

8. The method of any of the preceding claim, wherein said growth disorder is selected from a group consisting of growth hormone insufficiency, growth hormone deficiency, Intrauterine Growth Retardation, prematurity, growth failure in children who were born small for gestational age, very low birth weight, skeletal abnormalities, chromosomal variations, chronic renal insufficiency related growth retardation, constitutional delay of growth, cystic fibrosis related growth retardation, idiopathic short stature, short stature due to glucocorticoid treatment in children, failure of growth catching for short premature children, or any other condition resulting in short stature.

9. The method of the preceding claims, wherein said FFA regulator is fibric acid, nicotinic acid, a fibric acid derivative or a nicotinic acid derivative.

10. The method of claims 9, wherein said FFA regulator is nicotinic acid or a nicotinic acid derivative.

11. The method of claim 10, wherein said FFA regulator is acipimox.

12. The method of any of the preceding claims, wherein said GH is administered by subcutaneous injection.

13. The method of any of the preceding claims, wherein said FFA regulator(s) is administered orally.

14. Use of a combination of growth hormone and at least one FFA regulator in the preparation of a medicament or composition for treating growth disorders in a juvenile.

15. Use of at least one FFA regulator in the preparation of a medicament for increasing the growth promoting effects of growth hormone therapy in a juvenile

16. Use of at least one FFA regulator in the preparation of a medicament for preventing or treating the adverse consequences of growth hormone treatment in a juvenile.

17. Use of at least one FFA regulator in the preparation of a medicament for preventing or treating oedema as an adverse consequences of growth hormone treatment in a mammal.

18. Use of at least one FFA regulator in the preparation of a medicament for preventing or treating trabecular bone loss associated with early stages of GH therapy as an adverse consequences of growth hormone treatment in a mammal.

19. Use according to any one of claim 16 to 18, wherein said mammal or juvenile suffers from a growth disorder.

20. The use of any one of claims 14 to 19, wherein said juvenile or said mammal is human.

21. The use of any of claims 14 to 20, wherein said growth disorder is selected from a group consisting of growth hormone insufficiency, growth hormone deficiency, Intrauterine Growth Retardation, prematurity, growth failure in children who were born small for gestational age, very low birth weight, skeletal abnormalities, chromosomal variations, chronic renal insufficiency related growth retardation, constitutional delay of growth, cystic fibrosis related growth retardation, idiopathic short stature, short stature due to glucocorticoid treatment in children, failure of growth catching for short premature children, or any other condition resulting in short stature

22. The use of any one of claims 15 to 21, wherein said medicament comprises a combination of said growth hormone and said FFA regulator(s).

23. The use of any one of claims 14 to 22, wherein said FFA regulator is fibric acid, nicotinic acid, a fibric acid derivative or a nicotinic acid derivative.

24. The use of claim 23, wherein said FFA regulator is nicotinic acid or a nicotinic acid derivative.

25. The use of claim 24, wherein said FFA regulator is acipimox.

26. A composition or medicament for treating growth disorders and /or preventing or treating the adverse consequences of growth hormone treatment, comprising growth hormone and at least one FFA regulator.

27. A composition according to claim 26, wherein said composition or medicament comprises a suitable pharmaceutical carrier and/or excipient for said growth hormone and/or said FFA regulator(s).

28. The composition of claim 26 or 27, wherein said FFA regulator is fibric acid or a fibric acid derivative.

29. The composition of claim 28, wherein said FFA regulator is fenofibrate.